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# Olmesartan-based monotherapy vs combination therapy in hypertension: A meta-analysis based on age and chronic kidney disease status

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Antihypertensive monotherapy is often insufficient to control blood pressure (BP). Several recent guidelines advocate for initial combination drug therapy in many patients. This meta-analysis of seven randomized, double-blind studies (N = 5888) evaluated 8 weeks of olmesartan medoxomil (OM)–based single-pill dual-combination therapy (OM+amlodipine/azelnidipine or hydrochlorothiazide) vs OM monotherapy in adults with hypertension. BP-lowering efficacy, goal achievement, and adverse events were assessed in the full cohort and subgroups (elderly/nonelderly and patients with and without chronic kidney disease). In the full cohort at week 8, for dual therapy vs monotherapy, seated BP was lower (137.5/86.1 mm Hg vs 144.4/89.9 mm Hg), and the mean change from baseline in BP and BP goal achievement (<140/90 mm Hg) were greater (−22.7/−15.0 mm Hg vs −16.0/−11.3 mm Hg and 51.2% vs 34.7%, respectively). Adverse events were similar between groups. BP-lowering efficacy among subgroups mirrored the findings in the full cohort whereby changes were significantly greater following OM dual-combination therapy vs OM monotherapy.

## 1 | INTRODUCTION

Hypertension is a well-known risk factor for cardiovascular disease and contributes to the incidence of heart disease, stroke, and kidney failure. Approximately one quarter of the adult population in most developed and developing communities has hypertension.[1] Guidelines for blood pressure (BP) goals are under debate in the face of organizational recommendations and recent clinical trial data. Recommendations from the Eighth Joint National Committee (JNC 8),[2] American Society of Hypertension (ASH)/International Society of Hypertension (ISH),[3] and the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines[4] are broadly similar. They recommend a target BP goal of <140/90 mm Hg for patients younger than 60 years or for those with comorbidities (chronic kidney disease [CKD], diabetes mellitus, or history of cardiovascular disease) and a target BP goal of <150/90 mm Hg for older patients (aged ≥60 years).

The options for treatment are generally well established. General recommendations from JNC 8, ASH/ISH, and ESH/ESC for initial pharmacologic therapy choices after the failure of lifestyle interventions include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, β-blockers, or thiazide-type diuretics.[2–4]

Monotherapy with an antihypertensive agent will only help about 17% to 23% of patients achieve their BP goal, and most patients will

require more than two drugs to achieve BP control.[5] Therefore, major hypertension treatment guidelines currently suggest that combination antihypertensive therapy be used initially, particularly for high-risk patients or those with very high baseline BP.[2,4] For the general population (all ages, including patients with diabetes mellitus but not CKD), JNC 8 specifically recommends that combination therapy be initiated with two drugs simultaneously (either as two separate pills or as a single-pill combination) if systolic BP is >160 mm Hg and/or diastolic BP is >100 mm Hg, or if systolic BP is >20 mm Hg above goal and/or diastolic BP is >10 mm Hg above goal.[2] Ongoing clinical trials, along with updated societal guidelines and meta-analyses of previously published studies, will continue to shape hypertension treatment recommendations in the future.

A large body of clinical trial data has demonstrated that the ARB olmesartan medoxomil (OM) is well tolerated and effective in reducing BP. OM has been shown to provide 24-hour BP-lowering coverage and has a safety profile similar to that of placebo when used as monotherapy or in combination therapy,[6] including when used across a wide range of patient subgroups (obese, elderly, children, black, Hispanic, or those with diabetes mellitus).[7-16] In light of the various recommendations from treatment guidelines and clinical trials, the current meta-analysis sought to compare the efficacy and safety of OM single-pill dual-combination therapy with that of OM monotherapy. Analyses were performed in the following subgroups of patients with hypertension: elderly, nonelderly, CKD, and non-CKD.

## 2 | MATERIALS AND METHODS

### 2.1 | Database definition and inclusion criteria

An integrated database of previously locked individual OM clinical trial databases was developed by Daiichi Sankyo, Inc. (Edison, NJ) for the purpose of completing a patient-level meta-analysis. The meta-analysis included completed studies sponsored by group companies of Daiichi Sankyo globally reporting the efficacy and safety of OM. Studies were included if they met the following criteria: randomized, double-blind, placebo- or active-controlled, phase 2 through 4 clinical trials and a scheduled double-blind treatment duration of ≥28 days for the entire period of parallel design or for the first crossover period. To be included in the meta-analysis, the studies had to have a double-blind period of at least 8 weeks including patients (aged ≥18 years) with hypertension in which randomized treatment consisted of either OM single-pill dual-combination therapy with amlodipine, azelnidipine, or hydrochlorothiazide compared with OM monotherapy, and have evaluated BP-lowering efficacy and BP goal achievement end points (Figure S1). Institutional review boards reviewed and approved study protocols per local regulations, and patients provided written informed consent for each individual study included in the meta-analysis.

### 2.2 | Assessments

Efficacy end points that were studied included mean seated BP (SeBP; included seated systolic BP [SeSBP] and seated diastolic BP) and change from baseline in mean SeBP at each time point (observed case approach) and end point (week 8; last-observation-carried-forward [LOCF] approach); and the proportion of patients achieving mean SeBP <140/90 mm Hg and SeSBP <140 mm Hg at end point (LOCF approach).

Comprehensive safety assessments reported the incidence of any treatment-emergent adverse event (TEAE) occurring within the first 8 weeks of the double-blind period or until permanent discontinuation of study medication, whichever occurred first, including those that were drug-related or serious, the number of deaths, and the incidence of individual TEAEs.

### 2.3 | Statistical analysis

The primary statistical analysis was based on the full analysis set, defined as all patients who received at least one dose of study medication and had a nonmissing baseline and at least one nonmissing postbaseline SeBP value. Subanalyses were performed on subgroups that comprised elderly (aged 60–79 years) and nonelderly (aged<60 years) patients and patients with CKD (estimated glomerular filtration rate <60 mL/min/1.73 $m^2$) and without CKD (estimated glomerular filtration rate ≥60 mL/min/1.73 $m^2$). For subgroup analyses of elderly/nonelderly patients and those with and without CKD, studies were excluded if they did not include both subgroups for direct comparison within studies. Frequency distributions and summary statistics for the various parameters were calculated separately by treatment group and time point. Mean values and change from baseline in SeSBP and seated diastolic BP are presented using the observed case approach at each time point and the LOCF approach at end point (week 8). SeBP goal data are reported from baseline to end point (LOCF). Results of the exploratory statistical analysis (two-way analysis of covariance with study and treatment as factors and baseline SeSBP as a covariate) of absolute change on mean SeSBP from baseline to end point (week 8; LOCF) are presented as forest plots.

## 3 | RESULTS

### 3.1 | Baseline characteristics

The integrated database consisted of 53 trials completed between 1996 and 2012 and represented 34 320 patients. Seven studies were included in the meta-analysis according to the inclusion criteria previously stated (Figure S1 and Table S1).[10,17-21] The full analysis set comprised 5888 patients (OM dual-combination therapy group, n = 3969; OM monotherapy group, n = 1919). Apparent differences between the baseline characteristics of the OM dual-combination therapy and OM monotherapy groups were small (Table 1); most patients were men and white with a mean (SD) age of 54.8 (10.7) years, mean (SD) body mass index of 29.7 (5.5) kg/$m^2$, and a mean SeBP of 160.2/101.1 mm Hg. At baseline, the mean estimated glomerular filtration rate was approximately 80.14 mL/min/1.73 $m^2$, and 12.6% of all patients had diabetes mellitus.

The demographics of individual subgroups mostly mirrored the characteristics of the full analysis set with the exception of the elderly

**TABLE 1** Baseline demographics

| Baseline demographics | Full analysis set (seven studies) | | Elderly subgroup (seven studies) | | Nonelderly subgroup (seven studies) | | CKD subgroup (seven studies) | | Non-CKD subgroup (seven studies) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OM mono (n = 1919) | OM dual (n = 3969) | OM mono (n = 587) | OM dual (n = 1314) | OM mono (n = 1316) | OM dual (n = 2631) | OM mono (n = 214) | OM dual (n = 428) | OM mono (n = 1705) | OM dual (n = 3540) |
| Age, mean (SD), y | 54.8 (10.8) | 54.9 (10.7) | 66.7 (4.8) | 66.0 (4.8) | 49.2 (7.5) | 49.0 (7.6) | 62.4 (10.4) | 62.4 (10.4) | 53.9 (10.5) | 53.9 (10.4) |
| Sex, No. (%) | | | | | | | | | | |
| Female | 873 (45.5) | 1753 (44.2) | 289 (49.2) | 613 (46.7) | 575 (43.7) | 1122 (42.6) | 140 (65.4) | 284 (66.4) | 733 (43.0) | 1469 (41.5) |
| Male | 1046 (54.5) | 2216 (55.8) | 298 (50.8) | 701 (53.3) | 741 (56.3) | 1509 (57.4) | 74 (34.6) | 144 (33.6) | 972 (57.0) | 2071 (58.5) |
| Race, No. (%) | | | | | | | | | | |
| White | 1541 (80.3) | 3193 (80.4) | 479 (81.6) | 1074 (81.7) | 1052 (79.9) | 2097 (79.7) | 169 (79.0) | 349 (81.5) | 1371 (80.4) | 2841 (80.3) |
| Asian | 228 (11.9) | 466 (11.7) | 85 (14.5) | 175 (13.3) | 138 (10.5) | 290 (11.0) | 2 (0.9) | 7 (1.6) | 225 (13.2) | 457 (12.9) |
| Black or African American | 125 (6.5) | 261 (6.6) | 19 (3.2) | 51 (3.9) | 105 (8.0) | 209 (7.9) | 42 (19.6) | 67 (15.7) | 83 (4.9) | 193 (5.5) |
| Other | 25 (1.3) | 49 (1.2) | 4 (0.7) | 14 (1.1) | 21 (1.6) | 35 (1.3) | 1 (0.5) | 6 (1.4) | 26 (1.5) | 49 (1.4) |
| BMI, mean (SD), $kg/m^2$ | 29.8 (5.6) | 29.7 (5.5) | 29.0 (5.5) | 28.9 (4.8) | 30.2 (5.7) | 30.1 (5.8) | 30.5 (5.3) | 30.3 (5.8) | 29.7 (5.7) | 29.6 (5.4) |
| SeSBP, mean (SD), mm Hg | 160.3 (13.9) | 160.2 (14.0) | 164.9 (14.4) | 163.9 (14.7) | 158.2 (13.0) | 158.2 (13.2) | 167.2 (17.0) | 166.1 (16.2) | 159.5 (13.2) | 159.5 (13.6) |
| SeDBP, mean (SD), mm Hg | 101.2 (5.8) | 101.1 (5.8) | 100.4 (5.8) | 100.5 (5.8) | 101.5 (5.7) | 101.4 (5.8) | 102.1 (6.0) | 101.8 (5.6) | 101.0 (5.7) | 101.0 (5.8) |
| Creatinine, mean (SD), mg/dL | 0.95 (0.20) | 0.96 (0.20) | 0.97 (0.21) | 0.98 (0.22) | 0.94 (0.19) | 0.95 (0.19) | 1.23 (0.22) | 1.24 (0.23) | 0.92 (0.16) | 0.93 (0.17) |
| eGFR, mean (SD), mL/min/1.73 $m^2$[a] | 80.46 (18.52) | 79.99 (18.44) | 75.00 (17.55) | 74.40 (17.17) | 83.03 (18.36) | 82.97 (18.35) | 53.52 (5.96) | 53.19 (6.17) | 83.84 (16.71) | 83.23 (16.71) |
| eGFR, No. (%) | | | | | | | | | | |
| >90 | 559 (29.1) | 1088 (27.4) | 117 (19.9) | 240 (18.3) | 441 (33.5) | 848 (32.2) | 0 (0.0) | 0 (0.0) | 559 (32.8) | 1088 (30.7) |
| >60 to ≤90 | 1146 (59.7) | 2452 (61.8) | 338 (57.6) | 804 (61.2) | 797 (60.6) | 1636 (62.2) | 0 (0.0) | 0 (0.0) | 1146 (67.2) | 2452 (69.3) |
| >45 to ≤60 | 191 (10.0) | 382 (9.6) | 118 (20.1) | 234 (17.8) | 71 (5.4) | 137 (5.2) | 191 (89.3) | 382 (89.3) | 0 (0.0) | 0 (0.0) |
| >30 to ≤45 | 22 (1.1) | 42 (1.1) | 14 (2.4) | 33 (2.5) | 7 (0.5) | 8 (0.3) | 22 (10.3) | 42 (9.8) | 0 (0.0) | 0 (0.0) |
| >15 to ≤30 | 1 (0.1) | 4 (0.1) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 1 (<0.1) | 1 (0.5) | 4 (0.9) | 0 (0.0) | 0 (0.0) |
| Missing data | 0 (0.0) | 1 (<0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (<0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diabetes mellitus, No. (%) | 228 (11.9) | 512 (12.9) | 95 (16.2) | 212 (16.1) | 132 (10.0) | 296 (11.3) | 30 (14.0) | 70 (16.4) | 198 (11.6) | 442 (12.5) |
| CHD, No. (%) | 110 (5.7) | 233 (5.9) | 62 (10.6) | 125 (9.5) | 48 (3.6) | 100 (3.8) | 24 (11.2) | 50 (11.7) | 86 (5.0) | 183 (5.2) |
| HF, No. (%) | 31 (1.6) | 69 (1.7) | 18 (3.1) | 35 (2.7) | 12 (0.9) | 32 (1.2) | 8 (3.7) | 19 (4.4) | 23 (1.3) | 50 (1.4) |
| High cardiovascular risk, No. (%) | 333 (17.4) | 729 (18.4) | 150 (25.6) | 320 (24.4) | 181 (13.8) | 398 (15.1) | 52 (24.3) | 111 (25.9) | 281 (16.5) | 618 (17.5) |

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; dual, dual therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; mono, monotherapy; OM, olmesartan medoxomil; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure.

[a]Based on the Modification of Diet in Renal Disease formula.

and patients with CKD whose mean baseline SeSBP values were slightly higher (Table 1). The rates of diabetes mellitus and high cardiovascular risk were higher among elderly patients compared with nonelderly patients. Similarly, compared with patients without CKD, the subgroup of patients with CKD had a higher incidence of diabetes mellitus, coronary heart disease, heart failure, and high cardiovascular risk.

## 3.2 | Efficacy

### 3.2.1 | Full analysis set

In the full analysis set, mean SeBP decreased rapidly towards the SeBP goal of <140/90 mm Hg within 2 weeks and was lower at end point (week 8) in the OM dual-combination therapy group compared with the OM monotherapy group (137.5/86.1 vs 144.4/89.9 mm Hg, respectively) (Figure 1A and Figure S2A). Corresponding mean SeBP changes from baseline at end point were −22.7/−15.0 mm Hg and −16.0/−11.3 mm Hg (Figure 2A and Figure S3A). The analysis of covariance of the absolute mean SeSBP change from baseline to end point showed an estimated overall treatment difference of 6.67 mm Hg (95% confidence interval [CI], 5.87–7.46) in favor of OM dual-combination therapy (Figure S4A).

### 3.2.2 | Elderly and nonelderly subgroups

The elderly and nonelderly subgroups comprised 1901 (OM dual-combination therapy, n = 1314; OM monotherapy, n = 587) and 3947 (OM dual-combination therapy, n = 2631; OM monotherapy, n = 1316) patients, respectively. Similar to the full analysis set, mean SeBP was lower in the OM dual-combination therapy vs the OM monotherapy groups at end point, irrespective of the age subgroup (elderly: dual-combination therapy, 141.1/85.4 mm Hg; monotherapy, 147.7/88.6 mm Hg; nonelderly: dual-combination therapy, 135.7/86.4 mm Hg; monotherapy, 142.7/90.5 mm Hg) (Figure 1B, Figure 1C, Figure S2B, and Figure S2C). Mean SeBP changes from baseline at end point in the two treatment arms were also comparable between the two age subgroups (Figure 2B, Figure 2C, Figure S3B, and Figure S3C). The analysis of covariance of the absolute mean SeSBP change from baseline to end point showed an estimated overall treatment difference of 6.25 mm Hg (95% CI, 4.76–7.74) in the elderly subgroup (Figure S4B) and 6.91 mm Hg (95% CI, 5.97–7.86) in the nonelderly subgroup (Figure S4C), both in favor of OM dual-combination therapy. Supplementary analysis using a revised threshold for elderly patients (aged ≥70 years) was performed to examine the effect of treatment in the older group. Baseline SeBP, mean SeBP change from baseline, and the proportion of patients achieving a BP goal of <140/90 mm Hg were similar between the ≥60- and ≥70-year age thresholds (Table S2).

### 3.2.3 | CKD and non-CKD subgroups

Of all patients in the full analysis set, 642 had CKD (OM dual-combination therapy, n = 428; OM monotherapy, n = 214) and 5245 patients were assigned to the non-CKD subgroup (OM dual-combination therapy, n = 3540; OM monotherapy, n = 1705). At study end, mean SeBP was lower among patients receiving OM dual-combination therapy compared with OM monotherapy (Figure 1D, Figure 1E, Figure S2D, and Figure S2E). Mean SeSBP at end point was higher in the CKD subgroup (OM dual-combination therapy, 141.8 mm Hg; OM monotherapy, 152.4 mm Hg) than in the non-CKD subgroup (OM dual-combination therapy, 137.0 mm Hg; OM monotherapy, 143.4 mm Hg). Compared with OM monotherapy, mean SeBP changes from baseline were greater among patients receiving OM dual-combination therapy in both the CKD and non-CKD subgroups. While the results for the CKD and non-CKD subgroups receiving OM monotherapy were similar (CKD, −14.9 mm Hg; non-CKD, −16.1 mm Hg), the mean SeBP change from baseline was larger among patients receiving OM dual-combination therapy in the CKD vs the non-CKD cohort (−24.3 vs −22.5 mm Hg, respectively) (Figure 2D and Figure 2E). The analysis of covariance of the absolute mean SeSBP change from baseline to end point showed an estimated overall treatment difference of 9.50 mm Hg (95% CI, 3.09–15.92) in the CKD cohort (Figure S4D) and 6.52 mm Hg (95% CI, 5.71–7.34) in the non-CKD cohort (Figure S4E) in favor of OM single-pill dual-combination therapy.

## 3.3 | BP goal achievement

While none of the trials were randomized to two different BP goals and evaluated cardiovascular outcomes, most studies in the integrated database targeted an SeBP goal of <140/90 mm Hg during the double-blind treatment period (Table S1). In the full analysis set, OM dual-combination therapy enabled a greater proportion of patients with hypertension to achieve an SeBP goal of <140/90 mm Hg or SeSBP goal of <140 mm Hg at end point compared with OM monotherapy (51.2% vs 34.7%, respectively [Figure 3A]; 58.4% vs 43.0% [Figure 3B]). The proportions of patients achieving SeBP and SeSBP goals were consistently higher with OM dual-combination therapy than with OM monotherapy across all patient subgroups (Figure 3).

More nonelderly vs elderly patients receiving OM dual-combination therapy achieved an SeBP goal of <140/90 mm Hg at end point (53.5% vs 47.1%, respectively) (Figure 3A). A greater proportion of patients receiving OM dual-combination therapy in the non-CKD subgroup achieved the SeBP goal of <140/90 mm Hg vs those in the CKD subgroup (52.4% vs 42.0%, respectively) (Figure 3A). As expected, similar trends were observed when examining the SeSBP goal of <140 mm Hg. Greater proportions of patients receiving OM dual-combination therapy in the nonelderly vs elderly subgroups (62.4% vs 51.0%, respectively) and non-CKD vs CKD subgroups (59.8% vs 46.7%, respectively) achieved the SeSBP goal at end point (Figure 3B).

## 3.4 | Safety

### 3.4.1 | Full analysis set

The proportion of patients experiencing any TEAE was comparable between the OM dual-combination therapy and OM monotherapy

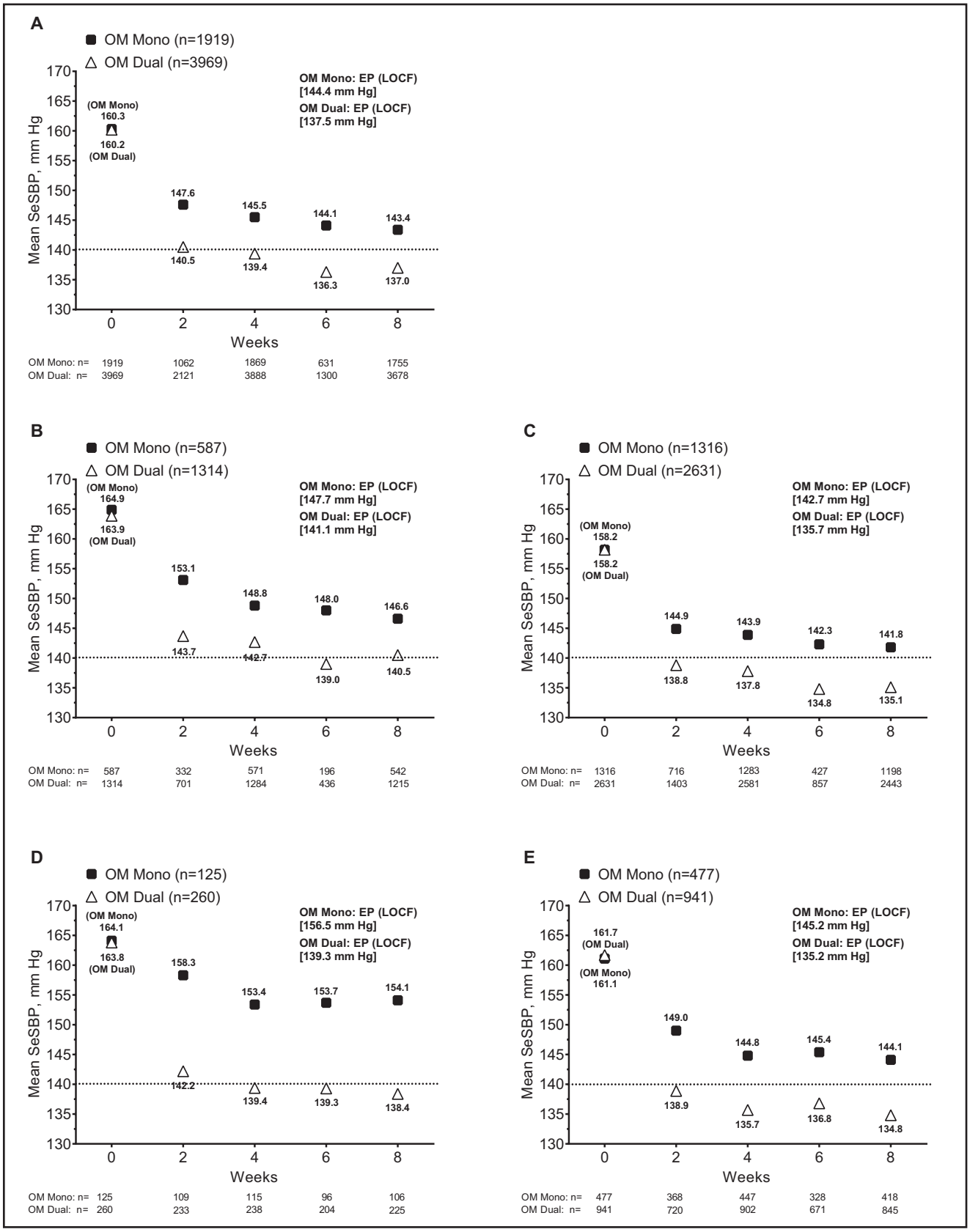


**FIGURE 1** Mean seated systolic blood pressure (SeSBP) from baseline to end point (EP; week 8, observed case approach) in olmesartan medoxomil (OM) monotherapy (Mono) vs dual-combination therapy (Dual) groups in patients with hypertension for the (A) full analysis set, (B) elderly subgroup, (C) nonelderly subgroup, (D) chronic kidney disease (CKD) subgroup, and (E) non-CKD subgroup. LOCF indicates last observation carried forward

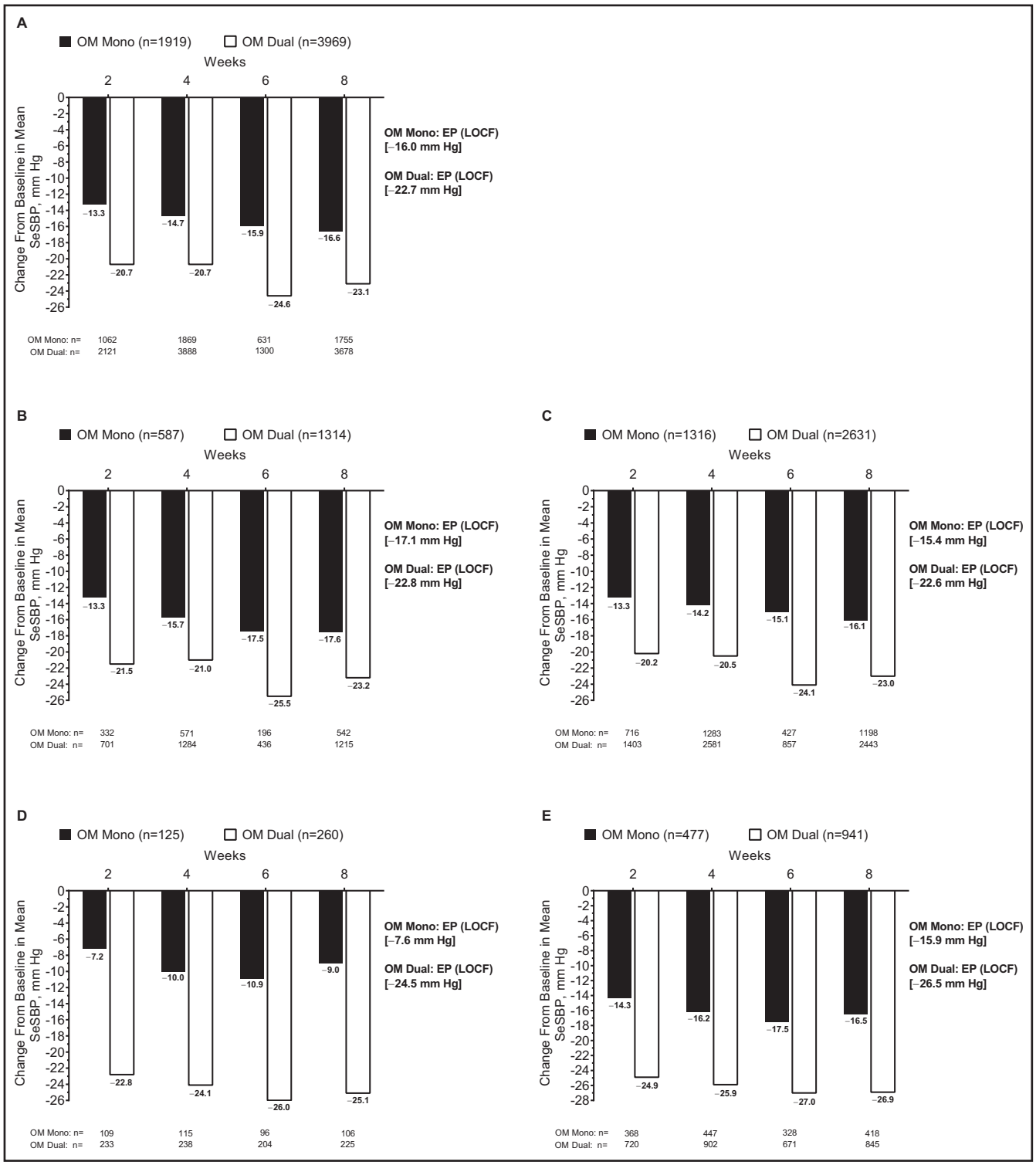


**FIGURE 2** Mean seated systolic blood pressure (SeSBP) change from baseline to end point (EP; week 8, observed case approach) in olmesartan medoxomil (OM) monotherapy (Mono) vs dual-combination therapy (Dual) groups in patients with hypertension for the (A) full analysis set, (B) elderly subgroup, (C) nonelderly subgroup, (D) chronic kidney disease (CKD) subgroup, and (E) non-CKD subgroup. LOCF indicates last observation carried forward

groups (28.9% vs 29.8%, respectively) (Table 2). The occurrence of serious TEAEs was also similar between groups (0.7% for both), whereas the proportions of patients with drug-related TEAEs were higher in the OM dual-combination therapy group than in the monotherapy group (10.2% vs 8.7%, respectively). No deaths were observed. The most frequently observed TEAEs were peripheral edema, headache, nasopharyngitis, dizziness, edema, fatigue, and back pain; however, the incidence of these individual events was

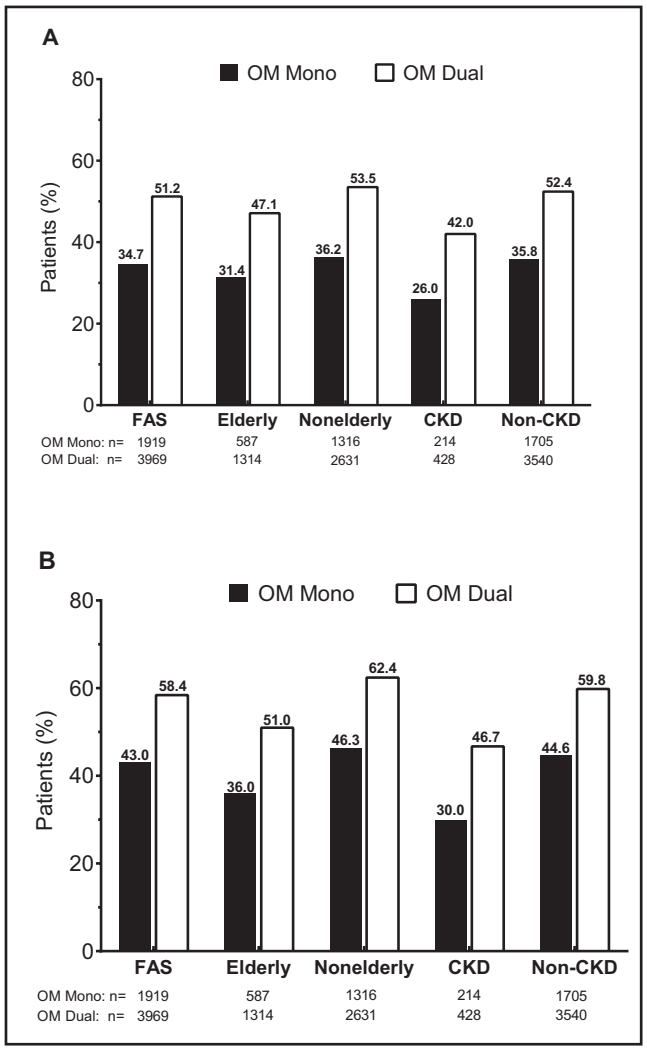


**FIGURE 3** Proportion of patients with hypertension in each subgroup analyzed receiving either olmesartan medoxomil (OM) monotherapy (Mono) or dual-combination therapy (Dual) and achieving the following goals: (A) seated blood pressure <140/90 mm Hg and (B) seated systolic blood pressure <140 mm Hg at week 8 (last-observation-carried-forward approach). CKD indicates chronic kidney disease; FAS, full analysis set

low and similar between the OM dual-combination therapy and OM monotherapy groups.

### 3.4.2 | Elderly and nonelderly subgroups

In the elderly subgroup, the incidence of any TEAE was lower in the OM dual-combination therapy group than in the OM monotherapy group (28.3% vs 32.2%, respectively) (Table 2). The incidence of serious TEAEs and drug-related TEAEs was similar between treatment groups. More elderly than nonelderly patients experienced a TEAE with OM monotherapy (32.2% vs 28.3%, respectively). The incidence of any TEAE was similar between elderly and nonelderly subgroups for patients treated with OM dual-combination therapy (28.3% vs 29.1%, respectively) (Table 2). Among the most frequently observed TEAEs in the full analysis set, there were no noticeable trends or differences when comparing treatment groups in the elderly vs nonelderly subgroups, with the exception of back pain with OM monotherapy (2.2% vs 0.8%, respectively).

### 3.4.3 | CKD and non-CKD subgroups

In the CKD subgroup, the incidence of any TEAE was higher in the OM monotherapy group than in the OM dual-combination therapy group (39.7% vs 32.9%, respectively) (Table 2). The incidence of serious TEAEs was similar between subgroups receiving monotherapy or dual-combination therapy. Compared with the non-CKD subgroup, the incidence of any TEAE and any drug-related TEAE was higher in the CKD subgroup (Table 2). More patients experienced peripheral edema and edema in the CKD subgroup vs the non-CKD subgroup, regardless of the treatment received (Table 2).

## 4 | DISCUSSION

Hypertension guidelines generally recommend starting patients with hypertension on monotherapy, with treatment options including angiotensin-converting enzyme inhibitors, ARBs, calcium channel blockers, thiazide-type diuretics, or a β-blocker. Guidelines such as those from ASH/ISH provide advice on specific drug selection by patient type.[3] If the initial treatment is not sufficient to achieve BP goals, patients may be prescribed a higher dose of monotherapy up to a maximum dose or will need a second agent from a different drug class added to the initial drug choice. Most patients are unable to achieve BP goals with monotherapy alone, and combination therapy with two or more agents may be necessary to achieve recommended BP goals.[5] The current meta-analysis examined the efficacy and safety of OM dual-combination therapy vs OM monotherapy to provide further information on whether initiating hypertension management with combination therapy may be the preferred treatment approach for patients with hypertension.

Despite slight variations in efficacy among the different patient populations examined in this meta-analysis, both OM dual-combination therapy and OM monotherapy achieved substantial BP reductions after 2 weeks of treatment, which were maintained through week 8. Compared with OM monotherapy, OM dual-combination therapy demonstrated greater BP-lowering efficacy, resulting in more patients achieving the target BP. This held true in the full analysis set and all subgroup populations analyzed. These results support a previous meta-analysis by Wald and colleagues,[22] which demonstrated the superior BP-lowering efficacy of combination therapy. Moreover, a retrospective analysis comparing combination antihypertensive therapy regimens vs monotherapy showed that patients who initially started on combination therapy were more likely to achieve BP goals after 12 months of therapy compared with patients who had started on monotherapy.[23] In light of these findings, initiating antihypertensive treatment with combination therapy may be preferred over initiating treatment with a single agent alone.

The prevalence of hypertension increases with age, being present in 65% of patients 60 years and older and in 76.5% of patients

**TABLE 2** TEAEs reported by ≥1% of patients in the OM monotherapy and single-pill dual-combination therapy groups for the full analysis set and elderly, nonelderly, CKD, and non-CKD subgroups

| | Full analysis set (seven studies) | | Elderly subgroup (seven studies) | | Nonelderly subgroup (seven studies) | | CKD subgroup (seven studies) | | Non-CKD subgroup (seven studies) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable, No. (%) | OM mono (n = 1919) | OM dual (n = 3969) | OM mono (n = 587) | OM dual (n = 1314) | OM mono (n = 1316) | OM dual (n = 2631) | OM mono (n = 214) | OM dual (n = 428) | OM mono (n = 1705) | OM dual (n = 3540) |
| Any TEAE | 571 (29.8) | 1146 (28.9) | 189 (32.2) | 372 (28.3) | 373 (28.3) | 766 (29.1) | 85 (39.7) | 141 (32.9) | 486 (28.5) | 1005 (28.4) |
| Any serious TEAE | 13 (0.7) | 28 (0.7) | 4 (0.7) | 14 (1.1) | 9 (0.7) | 14 (0.5) | 3 (1.4) | 5 (1.2) | 10 (0.6) | 23 (0.7) |
| Any drug-related TEAE | 166 (8.7) | 403 (10.2) | 49 (8.4) | 121 (9.2) | 113 (8.6) | 279 (10.6) | 33 (15.4) | 69 (16.1) | 133 (7.8) | 334 (9.4) |
| Serious drug-related TEAE | 1 (0.1) | 1 (<0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (<0.1) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Deaths | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| TEAEs reported by ≥1% of patients in the full analysis set[a] | | | | | | | | | | |
| Edema, peripheral | 56 (2.9) | 140 (3.5) | 16 (2.7) | 50 (3.8) | 38 (2.9) | 88 (3.3) | 10 (4.7) | 31 (7.2) | 46 (2.7) | 109 (3.1) |
| Headache | 79 (4.1) | 110 (2.8) | 21 (3.6) | 30 (2.3) | 56 (4.3) | 80 (3.0) | 12 (5.6) | 9 (2.1) | 67 (3.9) | 101 (2.9) |
| Nasopharyngitis | 49 (2.6) | 119 (3.0) | 14 (2.4) | 43 (3.3) | 33 (2.5) | 74 (2.8) | 2 (0.9) | 3 (0.7) | 47 (2.8) | 116 (3.3) |
| Dizziness | 31 (1.6) | 73 (1.8) | 13 (2.2) | 23 (1.8) | 18 (1.4) | 49 (1.9) | 3 (1.4) | 3 (0.7) | 28 (1.6) | 70 (2.0) |
| Edema | 10 (0.5) | 55 (1.4) | 3 (0.5) | 16 (1.2) | 7 (0.5) | 38 (1.4) | 3 (1.4) | 14 (3.3) | 7 (0.4) | 41 (1.2) |
| Back pain | 25 (1.3) | 38 (1.1) | 13 (2.2) | 18 (1.4) | 11 (0.8) | 20 (0.8) | 9 (4.2) | 4 (0.9) | 16 (0.9) | 34 (1.0) |
| Fatigue | 15 (0.8) | 43 (1.1) | 5 (0.9) | 11 (0.8) | 10 (0.8) | 32 (1.2) | 3 (1.4) | 6 (1.4) | 12 (0.7) | 37 (1.1) |

Abbreviations: CKD, chronic kidney disease; dual, dual therapy; mono, monotherapy; OM, olmesartan medoxomil; TEAE, treatment-emergent adverse event.

[a]By preferred term and primary system organ class.

80 years and older.[24] The ESH/ESC guidelines recommend the use of diuretics and calcium channel blockers for treating isolated systolic hypertension in the elderly.[4] In this meta-analysis, elderly patients aged 60 to 79 years who received OM dual-combination therapy achieved numerically similar SeSBP reductions compared with nonelderly patients. Additional supplemental analyses demonstrated similar trends in the efficacy of OM dual-combination therapy and monotherapy among patients 70 years and older vs those 60 years and older. Taken together, these results suggest that OM has utility in older patients and may be considered as a suitable initial therapy for the treatment of hypertension.

Hypertension and CKD are closely related conditions.[25] The prevalence of hypertension is even greater among patients with CKD than in the general population.[26] Consistent with the results observed in the full analysis set, OM dual-combination therapy was associated with greater improvements than OM monotherapy among patients with and without CKD. However, the magnitude of treatment response was smaller in the CKD vs the non-CKD subgroup, and a smaller proportion of patients with CKD achieved BP goals.[11]

A previous meta-analysis by Wang and colleagues[27] showed no association between OM and an increased risk of adverse events compared with other ARBs (losartan, candesartan, valsartan, and irbesartan). In the current analysis, both OM dual-combination therapy and OM monotherapy were well tolerated in all patients examined, and there were no unexpected safety concerns. A higher proportion of TEAEs and drug-related TEAEs was reported in the CKD subgroup than in the full analysis set for both treatment regimens. While this might be expected among a cohort of patients with a high burden of comorbidities, it is unclear whether this difference is clinically relevant because of the smaller number of patients in the CKD subgroup.

Recent clinical trials evaluating outcomes support the enhanced efficacy of combination therapy for the treatment of hypertension or high BP, albeit with mixed results for their primary end points. The SPRINT (Systolic Blood Pressure Intervention Trial) study demonstrated a significant reduction in the risk of major cardiovascular events when previously treated patients with high-risk hypertension were treated to an intensive BP goal of <120 mm Hg vs <140 mm Hg; however, this was achieved by approximately one more medication over those patients treated to the more conservative goal (2.8 vs 1.8 medications, respectively).[28] The HOPE-3 (Heart Outcomes Prevention Evaluation-3) study in patients with intermediate cardiovascular risk (≈40% with baseline hypertension) revealed that a combination of the ARB candesartan and hydrochlorothiazide lowered BP (−10.0/−5.7 mm Hg) but did not decrease the risk of major cardiovascular events over placebo.[29] In subgroup analysis, patients in the upper third of baseline systolic BP (>143.5 mm Hg) showed a significantly decreased risk in major cardiovascular events.[29]

## 5 | STUDY STRENGTHS AND LIMITATIONS

A major strength of this meta-analysis was the large sample size of patients in the full analysis set and elderly/nonelderly subgroups taken from pooled randomized controlled trials. While the definition of elderly used in this analysis (aged ≥60 years) differs from some organizational guidelines, supplemental analyses examining an alternative definition of elderly (aged ≥70 years) suggested little difference in the efficacy of OM dual-combination or monotherapy. A limitation to this meta-analysis was the short duration of the study, which was not extensive enough to identify rare serious adverse events.

## 6 | CONCLUSIONS

In this patient-level meta-analysis of randomized, double-blind, placebo- or active-controlled, phase 2 to 4 clinical trials in patients with hypertension, OM single-pill dual-combination therapy was well tolerated and more effective in lowering BP than OM monotherapy, enabling more patients to achieve guideline-recommended BP goals with a preferable safety profile.

### CONFLICT OF INTEREST

PD has served as a consultant for Amgen, Daiichi Sankyo, Inc., and Novartis. MW has served as a consultant for Allergan, Daiichi Sankyo, Inc., and Novartis; received research support from Servier; and served as a speaker for The Menarini Group and Merck Sharp and Dohme Corp. PER is an employee of Daiichi Sankyo Europe GmbH. GB has acted as a clinical trial investigator for AbbVie, Bayer, and Janssen; as a consultant for AbbVie, Bayer, and GlaxoSmithKline; and is an editor for the *American Journal of Nephrology*, *Diabetes Care: Hypertension Research*, and *UpToDate: Nephrology and Hypertension*.

### AUTHOR CONTRIBUTIONS

PD was involved in performing analyses, interpretation of results, and providing feedback in the drafting and editing of the article. MW was involved in performing analyses, interpretation of results, and providing feedback in the drafting and editing of the article. PER performed the identification of studies for the integrated database and for the subgroups in the meta-analysis, performed statistical analyses, and provided feedback in the drafting and editing of the article. GB was involved in interpretation of results and providing feedback in the drafting and editing of the article.

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### REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217-223.
2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the

panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.
3. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014;16:14-26.
4. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159-2219.
5. Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am J Hypertens*. 2001;14:241-247.
6. Redon J, Fabia MJ. Efficacy in angiotensin receptor blockade: a comparative review of data with olmesartan. *J Renin Angiotensin Aldosterone Syst*. 2009;10:147-156.
7. Chrysant SG, Izzo JL Jr, Kereiakes DJ, et al. Efficacy and safety of triple-combination therapy with olmesartan, amlodipine, and hydrochlorothiazide in study participants with hypertension and diabetes: a subpopulation analysis of the TRINITY study. *J Am Soc Hypertens*. 2012;6:132-141.
8. Chrysant SG, Lee J, Melino M, Karki S, Heyrman R. Efficacy and tolerability of amlodipine plus olmesartan medoxomil in patients with difficult-to-treat hypertension. *J Hum Hypertens*. 2010;24:730-738.
9. Chrysant SG, Littlejohn T 3rd, Izzo JL Jr, et al. Triple-combination therapy with olmesartan, amlodipine, and hydrochlorothiazide in black and non-black study participants with hypertension: the TRINITY randomized, double-blind, 12-week, parallel-group study. *Am J Cardiovasc Drugs*. 2012;12:233-243.
10. Hazan L, Hernandez Rodriguez OA, Bhorat AE, et al. A double-blind, dose-response study of the efficacy and safety of olmesartan medoxomil in children and adolescents with hypertension. *Hypertension*. 2010;55:1323-1330.
11. Kereiakes DJ, Chrysant SG, Izzo JL Jr, et al. Olmesartan/amlodipine/hydrochlorothiazide in participants with hypertension and diabetes, chronic kidney disease, or chronic cardiovascular disease: a subanalysis of the multicenter, randomized, double-blind, parallel-group TRINITY study. *Cardiovasc Diabetol*. 2012;11:134.
12. Lewin AJ, Kereiakes DJ, Chrysant SG, et al. Triple-combination treatment with olmesartan medoxomil/amlodipine/hydrochlorothiazide in Hispanic/Latino patients with hypertension: the TRINITY study. *Ethn Dis*. 2014;24:41-47.
13. Nesbitt S, Shojaee A, Maa JF. Efficacy/safety of a fixed-dose amlodipine/olmesartan medoxomil-based treatment regimen in hypertensive blacks and non-blacks with uncontrolled BP on prior antihypertensive monotherapy. *J Clin Hypertens (Greenwich)*. 2013;15:247-253.
14. Nesbitt SD, Shojaee A, Maa JF, Weir MR. Efficacy of an amlodipine/olmesartan treatment algorithm in patients with or without type 2 diabetes and hypertension (a secondary analysis of the BP-CRUSH study). *J Hum Hypertens*. 2013;27:445-452.
15. Roth EM, Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Olmesartan/amlodipine/hydrochlorothiazide in obese participants with hypertension: a TRINITY subanalysis. *J Clin Hypertens (Greenwich)*. 2013;15:584-592.
16. Weir MR, Shojaee A, Maa JF. Efficacy of amlodipine/olmesartan medoxomil ± hydrochlorothiazide in patients aged ≥ 65 or < 65 years with uncontrolled hypertension on prior monotherapy. *Postgrad Med*. 2013;125:124-134.
17. Armstrong C. JNC8 guidelines for the management of hypertension in adults. *Am Fam Physician*. 2014;90:503-504.
18. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2009-2020.
19. Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: the TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther*. 2010;32:1252-1269.
20. Lacourciere Y, Crikelair N, Glazer RD, Yen J, Calhoun DA. 24-Hour ambulatory blood pressure control with triple-therapy amlodipine, valsartan and hydrochlorothiazide in patients with moderate to severe hypertension. *J Hum Hypertens*. 2011;25:615-622.
21. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-2116.
22. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290-300.
23. Byrd JB, Zeng C, Tavel HM, et al. Combination therapy as initial treatment for newly diagnosed hypertension. *Am Heart J*. 2011;162:340-346.
24. Fogari R, Taddei S, Holm-Bentzen M, Baszak J, Melani L, Schumacher K. Efficacy and safety of olmesartan medoxomil 40 mg/hydrochlorothiazide 12.5 mg combination therapy versus olmesartan medoxomil 40 mg monotherapy in patients with moderate to severe hypertension: a randomized, double-blind, parallel-group, multicentre, multinational, phase III study. *Clin Drug Investig*. 2010;30:581-597.
25. Judd E, Calhoun DA. Management of hypertension in CKD: beyond the guidelines. *Adv Chronic Kidney Dis*. 2015;22:116-122.
26. Garimella PS, Uhlig K. Current issues in the management and monitoring of hypertension in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2013;22:599-606.
27. Wang L, Zhao JW, Liu B, Shi D, Zou Z, Shi XY. Antihypertensive effects of olmesartan compared with other angiotensin receptor blockers: a meta-analysis. *Am J Cardiovasc Drugs*. 2012;12:335-344.
28. Barrios V, Brommer P, Haag U, Calderon A, Escobar C. Olmesartan medoxomil plus amlodipine increases efficacy in patients with moderate-to-severe hypertension after monotherapy: a randomized, double-blind, parallel-group, multicentre study. *Clin Drug Investig*. 2009;29:427-439.
29. Ogihara T, Saruta T, Rakugi H, et al. Rationale, study design, and implementation of the COLM study: the combination of OLMesartan and calcium channel blocker or diuretic in high-risk elderly hypertensive patients. *Hypertens Res*. 2009;32:163-167.

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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